Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M(+) diffuse midline gliomas.

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Public Summary:
Diffuse intrinsic pontine glioma (DIPG) and other diffuse midline gliomas (DMGs) with mutated histone H3 K27M (H3-K27M)(1-5) are aggressive and universally fatal pediatric brain cancers (6) . Chimeric antigen receptor (CAR)-expressing T cells have mediated impressive clinical activity in B cell malignancies(7-10), and recent results suggest benefit in central nervous system malignancies(11-13). Here, we report that patient-derived H3-K27M-mutant glioma cell cultures exhibit uniform, high expression of the disialoganglioside GD2. Anti-GD2 CAR T cells incorporating a 4-1BBz costimulatory domain (14) demonstrated robust antigen-dependent cytokine generation and killing of DMG cells in vitro. In five independent patient-derived H3-K27M(+) DMG orthotopic xenograft models, systemic administration of GD2-targeted CAR T cells cleared engrafted tumors except for a small number of residual GD2(lo) glioma cells. To date, GD2-targeted CAR T cells have been well tolerated in clinical trials(15-17). Although GD2-targeted CAR T cell administration was tolerated in the majority of mice bearing orthotopic xenografts, peritumoral neuroinflammation during the acute phase of antitumor activity resulted in hydrocephalus that was lethal in a fraction of animals. Given the precarious neuroanatomical location of midline gliomas, careful monitoring and aggressive neurointensive care management will be required for human translation. With a cautious multidisciplinary clinical approach, GD2-targeted CAR T cell therapy for H3-K27M(+) diffuse gliomas of pons, thalamus and spinal cord could prove transformative for these lethal childhood cancers.

Scientific Abstract:
Diffuse intrinsic pontine glioma (DIPG) and other diffuse midline gliomas (DMGs) with mutated histone H3 K27M (H3-K27M)(1-5) are aggressive and universally fatal pediatric brain cancers (6) . Chimeric antigen receptor (CAR)-expressing T cells have mediated impressive clinical activity in B cell malignancies(7-10), and recent results suggest benefit in central nervous system malignancies(11-13). Here, we report that patient-derived H3-K27M-mutant glioma cell cultures exhibit uniform, high expression of the disialoganglioside GD2. Anti-GD2 CAR T cells incorporating a 4-1BBz costimulatory domain (14) demonstrated robust antigen-dependent cytokine generation and killing of DMG cells in vitro. In five independent patient-derived H3-K27M(+) DMG orthotopic xenograft models, systemic administration of GD2-targeted CAR T cells cleared engrafted tumors except for a small number of residual GD2(lo) glioma cells. To date, GD2-targeted CAR T cells have been well tolerated in clinical trials(15-17). Although GD2-targeted CAR T cell administration was tolerated in the majority of mice bearing orthotopic xenografts, peritumoral neuroinflammation during the acute phase of antitumor activity resulted in hydrocephalus that was lethal in a fraction of animals. Given the precarious neuroanatomical location of midline gliomas, careful monitoring and aggressive neurointensive care management will be required for human translation. With a cautious multidisciplinary clinical approach, GD2-targeted CAR T cell therapy for H3-K27M(+) diffuse gliomas of pons, thalamus and spinal cord could prove transformative for these lethal childhood cancers.